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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,440	11/15/2001	David Botstein	P2730P1C31	3276

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,440	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment and Remarks, submitted 24 July 2007, have been entered.

Claims 119-126 and 129-131 are under consideration in the instant office action.

New rejections

Claim Rejections-35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. This rejection was made in previous Office Actions and then withdrawn in error in the Office Action of 30 May 2007

The basis of the rejections is solely that **gene amplification levels** are not predictive of mRNA or polypeptide levels. In the interest of clarity, the basis of the rejections is set forth thusly:

The claims are directed to the polypeptide of SEQ ID NO: 351, wherein the encoding nucleic acid is amplified in lung cell carcinomas. The claims do not require that the nucleic acid encoding the claimed polypeptide be overexpressed in any tumor, or that the polypeptides have any biological activity. Claims are also presented to polypeptides having 80-99% sequence identity to SEQ ID NO: 351, SEQ ID NO: 351 lacking its signal peptide, and peptides encoded by the DNA deposited under accession number 209982. The specification discloses the claimed polypeptide of SEQ ID NO: 351, also known as PRO1153. Applicants have gone on the record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See the Remarks received 25 June 2004, p. 11.

At pages 544-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1153 had a ΔCt value of at least 1.0 for two out of fourteen lung tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 544, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative

number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 544, it is stated that samples were used if their values were within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 540-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

Firstly, there are several problems with the data provided in this example. Only two out of the fourteen lung cancer samples tested positive. Therefore, if a sample were taken from an individual with actual lung cancer, ***it is more likely than not that this assay would yield a false negative result***. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which results in aneuploidy **before** the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952: 1-12, of record, especially p. 4, Figure 4) who teach that damaged, precancerous lung epithelium is often aneuploid. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus, it is not clear that PRO1153 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO1153 is a diagnostic probe for lung cancer unless it is clear that PRO1153 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Secondly, in order for PRO1153 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1153 mRNA or PRO1153 polypeptide levels in lung tumors have

been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722, of record), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (p. 14722, second paragraph of left column; pp. 14720-14721)

Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state: "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

The *general* concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88, of record). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33): 21161-21168, of record) speak to the general lack of correlation between gene

amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.***" (Emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the *latter three genes are probably incidentally included in the amplicons*." (Emphasis added). There is no evidence in the instant application that PRO1153 confers any growth advantage to a cell; thus it cannot be presumed that the encoded protein is overexpressed simply because the genomic DNA, including the gene being studied, is amplified.

An additional reference that provides evidence that gene amplification does not generally

lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635, of record). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*" Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO1153.

Therefore, data pertaining to PRO1153 genomic DNA do not indicate anything significant regarding the encoded PRO1153 polypeptides. The data do not support the specification's assertion that PRO1153 can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO1153 is overexpressed in any cancer to the extent that it could be used as cancer diagnostic agent; thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1153 nucleic acid or polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of PRO1153 as a diagnostic marker and therapeutic tool is simply a starting point for further research and investigation into the potential practical uses of the nucleic acids. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), the Court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the

> public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are properly reintroduced.

Maintained Rejections

Claim Rejections - 35 USC § 112, Written Description

Claims 119-123 are rejected are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims are presented to isolated "native sequence" polypeptides having 80-99% sequence identity to SEQ ID NO: 351. Applicants amended the independent claims to specify that the polypeptides are amplified in "adenocarcinomas or squamous cell carcinomas of the lung." (25 June 2004).

The specification teaches a polypeptide (SEQ ID NO: 351). However, the specification does not teach functional or structural characteristics of all claimed polypeptides. The description of one PRO polypeptide (SEQ ID NO: 351) is not adequate written description of an

entire genus of polypeptides.

It is noted that at pages 2-4 of the Remarks, Applicants cite pertinent case law reviewing the legal standard of written description. The Examiner takes no issue with Applicants' general comments regarding the legal standard for written description.

Applicants submit that the instant specification evidences the actual reduction to practice of a full-length PRO1153 polypeptide of SEQ ID NO: 351. Thus, the genus of the polypeptides with at least 80% sequence identity to SEQ ID NO: 351, which possesses the functional property of having a nucleic acid which is overexpressed in adenocarcinomas or squamous cell carcinomas of the lung, would meet the requirement of 35 U.S.C.§ 112, first paragraph as providing adequate written description. Applicants submit that the specification describes methods for the *determination* of percent identity between two amino acid sequences. They also state that one of ordinary skill in the art would have understood at the time of filing what was encompassed by the claims.

Applicants' arguments have been fully considered, but are not found to be persuasive. Specifically, Applicants have not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 351, that still retain the function of SEQ ID NO: 351. Nor has Applicant described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 351, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 351. Applicants have not described or shown possession of any polypeptide sequence 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 351 that occurs in nature or how to identify such. Even one skilled in the art could not envision the detailed chemical structure of all or a significant number of

encompassed PRO1153 polypeptides, and therefore, would not know how to make or use them. The specification of the instant application only teaches a PRO1153 polypeptide of SEQ ID NO: 351. However, the description of one PRO1153 polypeptide species (SEQ ID NO: 351) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all sequences found in nature, as well as variants, fragments, and derivatives wherein the nucleic acid encoding the protein is overexpressed in lung tumor cells. Additionally, a method of calculating the percentage identity is not equivalent to a method of making, and it does not provide sufficient description for the instantly claimed genus of PRO1153 polypeptide variants. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound *itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The courts have specifically stated that if the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide, until the structure is disclosed, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or production. Applicants submit that Fiers *v. Revel* and *Amgen Inc. v. Chugai* do not apply to the claimed polypeptides, because they dealt with written description of DNA (Remarks, p. 4). They also cite Enzo Biochem., v. Genprobe, Inc. in which the court adopted the standard that "the written description can be met by showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics,..., i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function or structure, or some

combination of such characteristics" (Id. at 1324). Applicants submit that while the invention in *Enzo* was still DNA, the holding has been treated as being applicable to proteins as well, and indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids. Applicants submit that current applicable case law holds that biological sequences are not adequately described solely by a description of their desired functional activities, and that the instant claims meet the standard set by the Enzo court in that the claimed sequences are defined not by functional properties, but also by structural limitations, since it is well established that a combination of functional and structural features may suffice to described a claimed genus.

Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the previous office actions. Eighty percent identity to a described sequence is not a true structural requirement. It is not disclosed which of the 80% of amino acids are important for activity. In addition, being overexpressed in tumors is not a functional property, but a characteristic.

Applicants indicate that the instant specification provides an assay for detecting the recited functional activity of the variant polypeptides and that procedures for making the claimed variant proteins are well known in the art and described in the specification. They argue that the claimed variant proteins possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO: 351.

Applicants' arguments have been fully considered but are not found to be persuasive. As discussed above, Applicants have not described or shown possession of a sufficient number of polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 351, that still retain

the function of SEQ ID NO: 351. The broad-brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No variants were made or shown to have activity, and no activity of the polypeptide of SEQ ID NO: 351 is disclosed. Only the PRO1153 polypeptide of SEQ ID NO: 351 is disclosed. Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

The skilled artisan cannot envision all possible PRO1153 polypeptides of the instant claims, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making. One cannot describe what one has not conceived. Adequate Written Description requires more than a mere statement that it is part of the invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. Accordingly, in the absence of sufficient recitation, and reduction to practice, of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Conclusion

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

SLW
2 October 2007

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646